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# Determination of components in traditional Chinese medicines associated with promoting or inhibiting urinary stone formation

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**Abstract** *Objective:* To measure oxalate, calcium, and sodium contents of traditional Chinese medicines (TCMs) that are commonly used to prevent and dissolve urinary stones to exclude the possibility that long-term use of such medicines promotes stone formation. The second objective was to measure citrate, potassium, and magnesium contents in the same medicines to provide possible clues about the mechanisms of prevention and dissolution of urinary stones by TCMs.
*Methods:* Ten of the most commonly-used TCMs for preventing and dissolving urinary stones were chosen and subjected to ion chromatography (IC) to measure water-soluble and total oxalate and citrate contents. Inductively coupled plasma atomic emission spectrometry (ICP-AES) was used to measure calcium, potassium, magnesium, and sodium contents in a water extract and in digestion liquid.
*Results:* Average contents of water-soluble oxalate, calcium, and sodium in the water extract were 41.92, 84.32, and 22.82 mg/100 g, respectively, far below the normal dietary intake of adults in China. The average contents of citrate and magnesium in water extracts were 268.99 and 66.65 mg/100 g, respectively, below the recommended intake for adults. These ion contents are therefore insufficient to inhibit the formation of urinary stones. The average content of potassium in the water extract was 867.71 mg/100 g, which was relatively abundant, so taking the prescription used in this experimental protocol can increase the body's potassium content to some extent.

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*Conclusions:* Long-term use of TCMs would not increase the risk of urinary stone formation. The potassium content in TCMs is high, which is one possible reason for the prevention of urinary stones by TCMs.


## Introduction

Traditional Chinese medicines (TCMs) have been used for centuries in China to prevent and treat urinary stones (calculi). In Chinese medicine, prevention and treatment of urinary calculi follow three modes of action: expulsion, prevention, and dissolution. Mechanisms for preventing stones may involve crystallization inhibition and formation of complexes with stone-causing substances. Dissolution of stones may mainly involve altering urinary pH.[1]

In using TCMs to prevent and dissolve urinary stones, long-term administration is typically required. Despite centuries' worth of empirical application of these TCMs, there has been a lack of systematic research into their specific mechanisms behind prevention and dissolution of stones and identifying their effective monomer components. There is little evidence in the literature that can exclude the possibility that long-term use of TCMs can promote urinary stone formation. Therefore, it is both necessary and useful to measure components in these TCMs that might promote or inhibit stone formation. In this study, we measured the oxalate, citrate, calcium, potassium, magnesium, and sodium contents in TCMs that are commonly used to prevent or dissolve urinary stones, to identify factors that might promote or inhibit stone formation. The results may prove useful in clinical practice and provide a theoretical foundation for application of TCMs in preventing and treating urinary stones.

## Materials and methods

### Materials

Samples: plantago seed (*Plantago asiatica* L.), mallow fruit (*Malvaverticillata* L.), lygodium spore [*Lygodiumjaponicum* (Thunb.) Sw.], talcum, lysimachia plant (*Lysimachiachristinae* Hance), glechoma aerial part [*Glechoma longituba* (Nakai) Kuprian.], malva nut [Scaphium scaphigerum (Wall. ex G. Don) G. Planch], pyrrosia leaf [*Pyrrosia lingua* (Thunb.) Farw.], water plantain rhizome (*Alisma plantago-aquatica* L.), and gizzard lining (*Gallus gallusdomesticus* Brisson). All the samples were purchased from Affiliated Hospital of Nanjing University of Traditional Chinese Medicine. The samples were confirmed by Pro. Xunhong Liu, who works at Nanjing University of Traditional Chinese Medicine.

### Instruments and reagents

The 883 Basic IC Plus ion chromatograph (Metrohm, Switzerland) was applied. OPTIMA5300DV inductively coupled plasma atomic emission spectrometer (PerkinElmer. Waltham, MA, USA). Sodium oxalate, sodium citrate, $Na_2CO_3$, NaOH, concentrated $HNO_3$, concentrated $HClO_4$, and concentrated HCl were of analytical grade. Ca, K, Mg, Na standard solutions (1000 mg/L) were produced by dissolving metal powder or metal oxide with a purity above 99.9% (mass fraction) in 1% $HNO_3$ solution (volume fraction), with dilution according to need. High purity, deionized water ($\geq$18.2 M$\Omega$) was used in all experiments.

### Experimental methods

#### Ion chromatography (IC) for measuring water-soluble oxalate and citrate content in TCMs

(1) Sample pretreatment: each sample was washed and dried [insolation and then oven-dried (60°C, 30 min)], then accurately weighed (5 g) and decocted (boiled) for 30 min in 500 mL of high purity water. The resultant decoction was strained, with both the filtrate and residue retained. The residue was decocted for 30 min in another 500 mL of water. This second decoction was strained, the filtrate retained, and the residue discarded. The two filtrate samples were combined by pouring into a volumetric flask making up to 1000 mL of liquid, which was reserved in a refrigerator at 4°C for experiments described below.
(2) 2 mL of the above extract was passed through a 0.25 μm microfiltration membrane, then water-soluble oxalate and citrate were measured by IC.
(3) Standard recovery tests: to examine the reliability of the method, standard recovery tests were conducted. Different amounts of oxalate and citrate standard solution were measured into a known amount of pyrrosia leaf extract, and standard recovery tests carried out.

#### IC to measure the total oxalate content in TCMs

To determine the total oxalate content, 10 mL of 0.5 mol/L HCl was added to 500 mL of pure water for sample pretreatment, then boiled for 30 min, together with the sample. Other steps were the same as above.

#### Inductively coupled plasma atomic emission spectrometry (ICP-AES) to measure calcium, potassium, magnesium, and sodium contents of the TCMs digestion liquid

(1) Sample pretreatment: the sample was washed and dried, then accurately weighed (5 g) into an

Erlenmeyer flask. $HNO_3$ (30 mL) and $HClO_4$ (10 mL) were added to the flask and left to stand overnight. The sample was ultrasonicated for 20 min, then slowly heated on a hot plate for digestion until the liquid was clear, and 1000 mL was placed in a volumetric flask. The liquid was stored in a refrigerator at 4°C until needed.

(2) 10 mL of the extract above was taken and the total calcium, potassium, magnesium, sodium contents measured directly by ICP-AES.

(3) Standard Recovery Tests: different amounts of Ca, K, Mg, Na standard solutions were added into a known amount of Folium Pyrrosiae, and standard recovery tests carried out. Measurements were repeated in triplicate, and the average calculated.

#### ICP-AES to measure calcium, potassium, magnesium, sodium contents in a water extract of a TCM

The method for measuring calcium, potassium, magnesium and sodium in a water extract involved the same sample pretreatment procedure as that used before measuring water-soluble oxalate and citrate acid. The other steps are the same as those used to measure calcium, potassium, magnesium, and sodium in the digestion liquid.

### Data processing

Microsoft Office Excel 2007 software was used for mean calculation, and demonstrating as mean (SD).

## Results

The water-soluble oxalate, total oxalate, and citrate contents in TCMs are shown in Table 1.

Calcium, potassium, magnesium, and sodium contents of $TCM_s$ in the water extract and digestion liquid are shown in Table 2.

**Table 1** Oxalate, citrate contents in TCMs used commonly for preventing and dissolving urinary stones.

| Medicine | Oxalate (mg/100 g) | | Citrate (mg/100 g) |
|---|---|---|---|
| | Water-soluble oxalate | Total oxalate | |
| Plantago seed | 52.66 | 85.48 | 39.56 |
| Mallow fruit | 44.10 | 57.84 | 87.76 |
| Lygodium spore | 4.34 | — | 88.98 |
| Talcum | 3.98 | — | 0.92 |
| Lysimachia plant | 46.14 | 472.42 | 870.02 |
| Glechoma aerial part | 6.54 | 8.34 | 175.46 |
| Malva nut | 102.86 | 125.50 | 602.12 |
| Pyrrosia leaf | 88.48 | 196.00 | 105.32 |
| Water plantain rhizome | 29.62 | 55.88 | 512.40 |
| Gizzard lining | 30.52 | 65.88 | 7.38 |
| Average | 41.92 | 147.17 | 268.99 |

Results of standard recovery tests for water-soluble oxalate, total oxalate, and citrate are shown in Table 3.

Results of standard recovery tests for calcium, potassium, magnesium, and sodium are shown in Table 4. Oxalate, citrate, calcium, potassium, magnesium, and sodium recoveries were between 96.51% and 107.94%, indicating that the two methods used were accurate and reliable, and enabled accurate quantitative analysis.

## Discussion

Ion chromatography (IC) is suitable for measuring low concentrations of anions and cations in aqueous solutions, and has wide applications in measuring organic acid content in plants. Low-molecular-weight organic acids within plants mainly exist in two forms: as free-state organic acids that are readily soluble in water and as organic salts that are combined with ions, while oxalate combined with calcium is insoluble in water. Water-insoluble organic acids can be extracted using HCl.[2] Oxalate and citrate are low-molecular-weight organic acids, so water extraction can measure the water-soluble oxalate and citrate contents, while extraction with HCl enables measurement of total oxalate content.

### ICP-AES

ICP-AES is an atomic emission spectroscopy analytical method that uses plasma as an excitation light source. It is commonly used in determination of elements contents in samples, and offers the advantages of high precision, low detection limits, a wide linear dynamic range and simultaneous determination of a variety of elements. Calcium, potassium, magnesium and sodium elements in plants exist partially in ionic form, and water extraction can measure the presence of the above elements in their ionic states. For elements in their non-ionic state, plants can be digested using concentrated $HNO_3$ and $HClO_4$, which can effectively eliminate interference from organic compounds, and total calcium, potassium, magnesium and sodium contents can be accurately measured in plants.

### Oxalate

Persons with excessive urinary excretion of oxalate (hyperoxaluria) are at high risk of forming calcium oxalate stones. Although only 10%—15% of urinary oxalate is derived from dietary intake, without metabolic abnormalities, the amount of oxalate absorbed intestinally is an important factor affecting urinary oxalate excretion. In healthy adults, oxalate intake and urinary oxalate excretion are positively correlated and hyperoxaluria patients are more sensitive to dietary oxalate.[3] Restricted intake of oxalate over the long term can maintain a lithiasis patient's urinary oxalate at a low level. Oxalate content is high in spinach, water spinach, leeks, tea, and other vegetables or plants, and is often greater than 150 mg/100 g.[4] In our study, average water-soluble oxalate content in each TCM was 41.92 mg/100 g, roughly equivalent to the content of napa cabbage (60 mg/100 g).[4] If all the TCMs in this study were combined into a prescription (each 10—20 g, total

**Table 2** Calcium, potassium, magnesium, and sodium content of TCMs used commonly for preventing and dissolving urinary stones.

| Medicinal | Water extract (mg/100 g) | | | | Digestion liquid (mg/100 g) | | | |
|---|---|---|---|---|---|---|---|---|
| | Calcium | Potassium | Magnesium | Sodium | Calcium | Potassium | Magnesium | Sodium |
| Plantago seed | 87.40 | 818.40 | 33.78 | 74.94 | 350.60 | 1072.20 | 226.80 | 94.94 |
| Mallow fruit | 10.82 | 507.20 | 13.14 | 11.40 | 140.72 | 550.00 | 236.20 | 18.84 |
| Lygodium spore | 31.80 | 504.60 | 45.24 | 13.82 | 189.00 | 776.80 | 156.04 | 22.42 |
| Talcum | 83.10 | 5.44 | 34.46 | 14.46 | 11,482.0 | 16.58 | 5698.00 | 25.62 |
| Lysimachia plant | 237.60 | 2486.0 | 150.54 | 21.66 | 1026.8 | 2815.40 | 254.40 | 35.40 |
| Glechoma aerial part | 141.26 | 2556.0 | 132.86 | 13.10 | 833.60 | 3058.80 | 315.40 | 33.12 |
| Malva nut | 51.90 | 657.00 | 88.54 | 8.70 | 202.20 | 830.00 | 245.00 | 16.64 |
| Pyrrosia leaf | 70.52 | 771.40 | 99.24 | 11.76 | 351.60 | 867.80 | 249.40 | 35.34 |
| Water plantain rhizome | 41.20 | 638.60 | 55.12 | 28.04 | 87.90 | 829.80 | 148.14 | 35.70 |
| Gizzard lining | 87.62 | 32.44 | 13.62 | 30.36 | 96.24 | 41.44 | 16.96 | 39.72 |
| Average | 84.32 | 897.71 | 66.65 | 22.82 | 1476.07 | 1085.88 | 754.63 | 35.77 |

**Table 3** Standard recovery tests for oxalate and citrate in pyrrosia leaf.

| | Water-soluble oxalate | | | Total oxalate | | | Citrate | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample volume (mg/100 g) | 88.48 | | | 196 | | | 105.32 | | |
| Added standard amount (mg/100 g) | 40 | 80 | 160 | 100 | 200 | 300 | 60 | 100 | 200 |
| Amount quantified (mg/100 g) | 129.08 | 169.84 | 251.34 | 298.62 | 404.78 | 511.56 | 170.30 | 211.74 | 305.94 |
| Recovery (%) | 100.68 | 101.54 | 103.23 | 101.34 | 104.48 | 107.94 | 104.73 | 106.10 | 100.59 |

100—200 g) to be taken every day, the amount of daily oxalate intake would be 41.92—83.84 mg. Even if calculated according to the average content of total oxalate, 147.17 mg/100 g, the daily intake of oxalate would be 147.17—294.34 mg. The daily adult intake of oxalate in western countries is 720—990 mg, while adults in India, where food is vegetable-based, ingest 810—2070 mg of oxalate each day.[4] Therefore, the oxalate content in the TCMs we analyzed is low and would not increase the risk of hyperoxaluria, even if taken over the long-term.

## Citrate

Citrate is an important inhibitor in urinary stone crystal formation because of its ability to chelate with calcium and reduce the saturation of calcium oxalate in urine. Citrate metabolism is rapid, so even when citrate intake is high over a short period, it is broken down quickly, and its concentration in the body does not increase. However, studies found that long-term intake of lemon or orange juice increases urine volume and urinary citrate excretion. Seltzer et al prescribed 12 patients with hypocitraturia to drink lemon juice (citrate 5900 mg/d) for 6 days.[5] The urinary citrate of 11 patients increased (average of 204 mg/d), and their urinary calcium excretion decreased to 30 mg/d, while urinary oxalate excretion was unchanged. Wabner et al compared orange juice (potassium 2340 mg, citrate 12,160 mg) with potassium citrate (6480 mg, potassium 2340 mg, citrate 3840 mg) to observe changes in urine composition, and found that orange juice can also increase urine pH and the excretion of urinary citrate (similar to potassium citrate).[6] In our study, the average content of citrate in each TCM was 268.99 mg/100 g. If all the TCMs in our study were combined into a prescription (each 10—20 g, total 100—200 g) to be taken every day, the daily intake of citrate would be 268.99—537.98 mg. Studies have found that the citrate content in lemon juice is 50,000 mg/L, in grapes 14,120 mg/L, and in orange juice 8972 mg/L.[7,8] Intake of citrate would be much higher than the combined total citrate levels of all the TCMs in our study, even if only 0.1 L of these juices were ingested daily. The citrate content in potassium citrate (at 6480 mg/d contains 3840 mg of citrate) is 10 times higher than that of the

**Table 4** Standard recovery tests for calcium, potassium, magnesium and sodium in Folium Pyrrosiae.

| | Water extract (mg/100 g) | | | | Digestion liquid (mg/100 g) | | | |
|---|---|---|---|---|---|---|---|---|
| | Ca | K | Mg | Na | Ca | K | Mg | Na |
| Sample volume | 70.52 | 771.40 | 99.24 | 11.76 | 351.60 | 867.80 | 249.40 | 35.34 |
| Adding standard amount | 100 | 800 | 100 | 10 | 300 | 800 | 300 | 30 |
| Measured value | 168.06 | 1584.20 | 206.80 | 21.44 | 665.40 | 1651.40 | 561.20 | 66.24 |
| Recovery rate | 96.51% | 101.66% | 107.62% | 97.28% | 103.92% | 98.11% | 104.73% | 102.55% |

combined total of the TCMs in this study. Thus, the citrate content in TCMs is too low to prevent the formation of urinary stones. Therefore, prevention of urinary stones by Chinese medicine may have nothing to do with their citrate content.

### Magnesium

Magnesium is also a crystallization inhibitor. It reduces urine calcium oxalate super saturation, thus inhibiting growth and aggregation of calcium oxalate crystals.[9] Studies found that supplementing magnesium to magnesium-deficient urinary stone patients can increase the excretion of urine citrate and magnesium, and decrease uric acid and calcium oxalate super saturation.[10] In this study, the average water extract magnesium content in the TCMs we analyzed was 66.65 mg/100 g. If all the TCMs were combined into a prescription (each 10–20 g, total 100–200 g) to be taken every day, the daily magnesium intake would be 66.65–133.30 mg. The recommended magnesium intake for adult men is 350 mg/d and for adult women, 300 mg/d.[11] Thus, if the TCMs in our study were taken in combination on a daily basis, they may supply additional magnesium to some extent, but not enough to validate the hypothesis that these TCMs can inhibit stone formation.

### Sodium

Studies have shown that a high sodium intake increases excretion of urine calcium, urine oxalate, uric acid, and reduces urinary citrate excretion.[12,13] Patients with urinary stones are typically advised not to exceed an intake of 2000 mg of sodium each day.[12] In our study, the average sodium content in a water extract of the TCMs we analyzed was22.82 mg/100 g. If all the TCMs in this study were combined into a prescription (each 10–20 g, total 100–200 g) to be taken every day, the daily intake of sodium would be 22.82–45.64 mg. If calculated according to the average content of sodium in the digestion solution, 35.77 mg/100 g, the daily sodium intake would be 35.77–71.54 mg, which is not even one-tenth of the daily intake limit of 2000 mg. Therefore, taking a prescription comprised of all the TCMs in this study would not increase the risk of stone formation through excessive sodium intake.

### Potassium

Inadequate potassium intake decreases urinary potassium, urinary citrate, urinary magnesium, urinary phosphate excretion, and increases super saturation of calcium oxalate.[14] Potassium intake can reduce urinary calcium excretion,[15] which could be caused by an increase in tubular reabsorption of calcium and phosphate. In addition, phosphate inhibits synthesis of 1,25-$(OH)_2D_3$, which reduces calcium absorption in the intestinal tract, and thereby reduce urinary calcium excretion. In this study, the average potassium content in the water extracts from TCM was 867.71 mg/100 g. If all the TCMs in this study were combined into a prescription (each 10–20 g, total 100–200 g) to be taken every day, the daily intake of potassium would be 867.71–1735.42 mg. Potassium citrate is a mainstay in the prevention of urinary stones. Taking potassium citrate at 5000 mg/d is equivalent to ingesting 1806 mg of potassium daily, which is similar to the total potassium intake in the TCMs in this study. The recommended intake of potassium in adults is 2000 mg/d.[11] Thus, if all the TCMs in our study were taken as a daily prescription on top of a normal diet, total potassium intake would be increased, which may be a possible explanation for the prevention of urinary stones by TCMs.

### Calcium

In the past, it was believed that calcium intake and calcium excretion were positively correlated, but recent studies suggest that a low calcium intake promotes oxalate absorption in the intestinal tract, causing hyperoxaluria, thus increasing the risk of urinary stone formation.[16] In addition, restriction of dietary calcium can stimulate secretion of vitamin D, causing a negative balance of calcium in bones, which increases urinary calcium excretion and thus the risk of urinary stone formation.[17] Therefore, restriction of dietary calcium in hypercalciuric patients who do not absorb calcium is not recommended. In our study, the average calcium content in the water extract of TCMs was84.32 mg/100 g. If all the TCMs in this study were combined into a prescription (each 10–20 g, total 100–200 g) to be taken every day, the daily intake of calcium would be 84.32–168.64 mg. The recommended calcium intake is 800–1200 mg/day in adults.[11] The total calcium content in all the TCMs that we evaluated would neither be a significant supplement of calcium nor a cause of hypercalciuria. Therefore, the intake of these TCMs combined, would have little effect on urinary calcium and would not increase the risk of urinary stone formation.

## Conclusions

The formation of urinary stones is highly related to diet, so dietary structure provides a baseline for determining the incidence of stones, with other factors acting as promoters or inhibitors on this basis. The TCMs that we evaluated contain a low content of promoting factors, such as oxalate, calcium and sodium, and thus would not increase the body's load of these factors, and even with long-term treatment would not increase the risk of stone formation. The contents of inhibitory factors, such as citrate and magnesium, are not high in these TCMs, and are insufficient for inhibiting the stone formation. However, the relatively high level of potassium in the TCMs may increase urinary pH and increase citrate excretion overlong-term use, which may be one of the possible reasons that these TCMs appear to inhibit development of urinary stones.

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